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EXAMINER	
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ART UNIT	PAPER NUMBER
1637	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/642,068	STUELPNAGEL ET AL.	
	Examiner	Art Unit	
	Teresa E. Strzelecka	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *April 9, 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-10,27-31 and 33-53* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-10,27-31 and 33-53* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This office action is in response to an amendment filed April 9, 2007. Claims 2-10, 27-31 and 33-37 were previously pending. Applicants amended claims 27-30 and 33-35 and added new claims 38-52. Applicants are notified that the newly added claims were misnumbered. The claim following claim 38 is numbered 49, it was re-numbered 39; there are two claims numbered 51, therefore the second was re-numbered 52, and claim 52 was renumbered as 53. This numbering is referred to in this office action. Claims 2-10, 27-31 and 33-53 are pending and will be examined.

2. Applicants' amendments overcame the following rejections: rejection of claims 2, 5-10, 27-31 and 33-37 under 35 U.S.C. 102(e) as anticipated by Lipshutz et al. as evidenced by Sinha et al.; rejection of claims 2, 5-7, 9, 27, 30, 31, 33 and 35-37 under 35 U.S.C. 102(e) as anticipated by Lam et al.; rejection of claims 3 and 4 under 35 U.S.C. 103(a) over Lipshutz et al. as evidenced by Sinha et al. and Nelson et al.

3. This office action contains new grounds for rejection necessitated by amendment. Applicant's arguments are moot in view of new grounds for rejection.

Claim interpretation

4. The following interpretation of claim limitations is used to evaluate correspondence between the current claims and prior art:

A) Applicants defined the term "pool" in the following way (page 8, last paragraph): "By "pool" is meant a plurality or more than one solution-phase oligonucleotide."

B) The term " first and second linkers" is interpreted as linkers which may be the same, as there is no requirement that they have to be different.

C) The term "chip" in claim 29 is interpreted as any substrate (it is used interchangeably with "substrate" in the claim. Applicants' definition on page 16, fourth paragraph: "... By "chip" or

biochip" herein is meant a planar substrate to which nucleic acids are directly or indirectly attached."

D) Applicants did not define the term "array" therefore any arrangement of oligonucleotides bound to a solid support is considered to be an array.

E) In view of the indefiniteness of claims 2-10, 27-31 and 33-53, the phrase "a substrate comprising at least first and second different oligonucleotides" is interpreted as the oligonucleotides on the substrate being either the same or different from the oligonucleotides released from a substrate.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 2-10, 27-31 and 33-53 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

As explained in the "Claim Interpretation" paragraph above, the first and second oligonucleotides in the contacting step can be interpreted as being either the same or different from the released first and second oligonucleotides. In case they are the same, the claims contain new matter, since there is no support in the disclosure for hybridization of the released, modified oligonucleotides to oligonucleotides with the same sequences.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 2-10, 27-31 and 33-53 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 2-10, 27-31 and 33-53 are indefinite in claims 27, 28, 29, 30, 33-35, 52 and 53. These claims recite two method steps which use an array of first and second different oligonucleotides: a step of releasing first and second oligonucleotides from a substrate and a step of contacting modified oligonucleotides with a substrate comprising first and second different oligonucleotides. It is not clear whether the first and second oligonucleotides in the contacting step are different from the first and second oligonucleotides released from a substrate.

B) Claim 52 is indefinite over the recitation of "contacting said first and second target nucleic acids in contact with said first and second target nucleic acids". It seems that one of the sets of first and second nucleic acids should be oligonucleotides.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the

contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 2, 5-10, 27-31 and 33-51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pastinen et al. (Genome Res., vol. 7, pp. 606-614, 1997) and Lipshutz et al. (U.S. Patent No. 6,013,440 A; cited in the previous office action), as evidenced by Sinha et al. (Nucl. Acids Res., vol. 12, pp. 4539-4557; cited in the previous office action).

Since claim 29 is specie of claims 27 and 30 and claims 33 and 35 are restated versions of claim 27, and claims 28 and 34 differ from claim 29 by the support being beads, only steps of claim 29 are discussed explicitly.

A) Regarding claims 2, 5-10, 27-31 and 33-51, Pastinen et al. teach minisequencing reactions on oligonucleotide arrays (Abstract), involving multiplex amplification of multiple targets using primer pairs (= modification of first and second oligonucleotides) and hybridization of the modified (= amplified) oligonucleotides to an array of oligonucleotides different from the first and second oligonucleotides for detection of single nucleotide polymorphisms (page 610, last two paragraphs; page 611; page 612; page 613, first paragraph; Fig. 2).

B) Pastinen et al. do not teach obtaining the primers from a pool of oligonucleotides released from a support it was synthesized on.

C) Lipshutz et al. teach a method of obtaining oligonucleotide pools.

Regarding claims 27-30 and 33-35, Lipshutz et al. teach multiplex detection of target nucleic acids, the method comprising:

a) providing an array comprising a substrate and a population of oligonucleotides, said population comprising at least first and second subpopulations, wherein said first subpopulation comprises at least a first oligonucleotide and, wherein said second subpopulation comprises at least a second oligonucleotide, wherein said first oligonucleotide is different from said second oligonucleotide and, wherein said first and second oligonucleotides are of known sequence, said first and second oligonucleotides being immobilized directly to said substrate through first and second cleavable linkers, respectively (Fig. 1; col. 2, lines 16-37 and 59-62; col. 3, lines 18-35; col. 6, lines 20-48; col. 21, lines 4-33);

b) cleaving said first and second linkers, thereby releasing said first and second subpopulations from said substrate thereby generating a pool of oligonucleotides comprising said first and second oligonucleotides (col. 2, lines 59-62; col. 21, lines 4-33); and

c) contacting said first and second oligonucleotides with a composition comprising at least a first and second target nucleic acid, whereby said first and second target nucleic acids hybridize with said first and second oligonucleotides whereby said target nucleic acids are detected (col. 2, lines 24-26; col. 3, lines 46-67; col. 4, lines 1-67; col. 5, lines 1-23; col. 7, lines 34-42; col. 8, lines 12-67; col. 9, lines 1-67; col. 10, lines 1-13).

Regarding claims 8, 28 and 34, Lipshutz et al. do not specifically teach the substrate being beads. However, they teach synthesis of oligonucleotides on controlled pore glass (CPG) (col. 21, line 7) and synthesis by the method of Sinha et al. (col. 20, lines 24, 25). Sinha et al. teaches synthesis of oligonucleotides on CPG beads (page 4544, last paragraph). Therefore, by teaching synthesis of oligonucleotides by the method of Sinha et al. Lipshutz et al. inherently teach synthesis on glass beads.

Regarding claim 2, Lipshutz et al. teach oligonucleotides with known sequences (col. 2, lines 18-22).

Regarding claims 5 and 31, Lipshutz et al. teach covalent attachment of oligonucleotides to the substrate (col. 17, lines 57-67; col. 18, lines 1-9; col. 21, lines 4-33).

Regarding claims 6 and 9, Lipshutz et al. teach synthesizing the oligonucleotides on a substrate (col. 16, lines 47-67; col. 17-19).

Regarding claim 7, Lipshutz et al. teach a substrate with a discrete sites (col. col. 16, lines 47-66).

Regarding claim 10, Lipshutz et al. teach printing and photolithography (col. 17, lines 18-67; col. 18-19).

Regarding claim 36, Lipshutz et al. teach glass (col. 17, lines 57, 58).

Regarding claim 37, Lipshutz et al. teach a chip (col. 17, lines 13-16 and 57-60).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used the oligonucleotide pools of Lipshutz et al. as primers in the mutation detection method of Pastinen et al. The motivation to do so, provided by Lipshutz et al., would have been that the pools were designed to bind to substantially every known nucleic acid sequence in a sample (col. 1, lines 12-18). The motivation to do so, provided by Pastinen et al., would have been that, as stated by Pastinen et al. (page 610, first paragraph):

"Despite the proceeding technical development related to miniaturized arrays for genotyping, a great challenge for the assays still lies in the sample preparation. At present, amplification of DNA templates by PCR limits the number of genomic fragments that can be analyzed efficiently. Methods are required by which a significantly larger number of fragments can be amplified or in which an amplification step is avoided."

Therefore, using the oligonucleotide pools of Lipshutz et al. would allow efficient multiplex amplification of target nucleic acids used for subsequent detection of SNPs.

12. Claims 3 and 4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pastinen et al. (Genome Res., vol. 7, pp. 606-614, 1997) and Lipshutz et al. (U.S. Patent No. 6,013,440 A; cited in the previous office action), as evidenced by Sinha et al. (Nucl. Acids Res., vol. 12, pp. 4539-4557; cited in the previous office action), as applied to claims 27-30 above, and further in view of Nelson et al. (Nucl. Acids Res., vol. 20, pp. 6253-6259 (1992).

A) Lipshutz et al. teach fluorescence detection of hybrids (col. 25, lines 43-46), but do not teach labeling of the synthesized oligonucleotides.

B) Regarding claims 3 and 4, Nelson et al. teach labeling oligonucleotides during the synthesis step using labeled phosphoramidites (Abstract; page 6255, last paragraph; page 6256, paragraphs 1-5; Table 1).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have labeled the oligonucleotides of Lipshutz et al. and Pastinen et al.using the method of Nelson et al. The motivation to do so, provided by Nelson et al., would have been that the oligonucleotides were used directly in PCR amplification and quantitation, mRNA isolation, FISH analysis, antisense gene regulation, DNA fragment analysis and triple helix formation (page 6258, last paragraph).

13. Claims 52 and 53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Beattie et al. (U.S. Patent No. 6,268,1467 B1) and Lipshutz et al. (U.S. Patent No. 6,013,440 A; cited in the previous office action), as evidenced by Sinha et al. (Nucl. Acids Res., vol. 12, pp. 4539-4557; cited in the previous office action).

A) Claims 52 and 53 are considered together in claim 53, since it is a species of claim 52. Regarding claims 52 and 53, Beattie et al. teach contacting multiple nucleic acid targets simultaneously with a multitude of detection probes and detection of the hybrids by binding of the hybrids to arrays of capture probes (Fig.1, 13-15; col. 7, lines 66, 67; col. 8, lines 1-63; col. 29, lines 1-67; col. 30, lines 1-30).

B) Beattie et al. teach using pools of oligonucleotides and chemical synthesis of oligonucleotides, but do not teach producing pools of oligonucleotides by cleaving oligonucleotides from an array.

C) Lipshutz et al. teach creation of oligonucleotide pools.

Regarding claims 52 and 53, Lipshutz et al. teach creation of oligonucleotide pools by:

a) providing an array comprising a substrate and a population of oligonucleotides, said population comprising at least first and second subpopulations comprising at least first and second different oligonucleotides, respectively, said first and second oligonucleotides being immobilized to first and second beads, respectively, through first and second cleavable linkers, respectively, said first and second beads being distributed on said substrate (Fig. 1; col. 2, lines 16-37 and 59-62; col. 3, lines 18-35; col. 6, lines 20-48; col. 21, lines 4-33. Lipshutz et al. do not specifically teach the substrate being beads. However, they teach synthesis of oligonucleotides on controlled pore glass (CPG) (col. 21, line 7) and synthesis by the method of Sinha et al. (col. 20, lines 24, 25). Sinha et al. teaches synthesis of oligonucleotides on CPG beads (page 4544, last paragraph). Therefore, by teaching synthesis of oligonucleotides by the method of Sinha et al. Lipshutz et al. inherently teach synthesis on glass beads.);

b) cleaving said first and second linkers, thereby releasing said first and second subpopulations from said first and second beads, thereby generating a pool of oligonucleotides

comprising said first and second different oligonucleotides (col. 2, lines 59-62; col. 21, lines 4-33); and

c) contacting said first and second oligonucleotides with a first and second target nucleic acid (col. 2, lines 24-26; col. 3, lines 46-67; col. 4, lines 1-67; col. 5, lines 1-23; col. 7, lines 34-42; col. 8, lines 12-67; col. 9, lines 1-67; col. 10, lines 1-13).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention oligonucleotide pools of Lipshutz et al. as probes in the mutation detection method of Beattie et al. The motivation to do so, provided by Lipshutz et al., would have been that the pools were designed to bind to substantially every known nucleic acid sequence in a sample (col. 1, lines 12-18). The motivation to do so, provided by Beattie et al., was stated by Beattie et al. (col. 5., lines 30-41):

"There is furthermore a need for improved techniques for analysis of nucleic acid samples of high genetic complexity, using sequence-targeted oligonucleotide array hybridization. Also, there is a need for improved profiling of gene expression using numerous oligonucleotide probes targeted to mRNA species. Moreover, there is a need for more efficient identification of species, strains and individuals using DNA probe arrays designed to hybridize with numerous unique nucleotide sequences. There is in addition a need to adapt oligonucleotide array hybridization to directly analyze nucleic acid samples without the use of additional steps of target sequence amplification, single strand isolation and labeling."

Therefore, the availability of oligonucleotide pools of Lipshutz et al. as probes in the detection method of Beattie et al. would allow efficient genotyping using microarrays.

14. No claims are allowed.

Conclusion

15. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Teresa E. Strzelecka whose telephone number is (571) 272-0789. The examiner can normally be reached on M-F (8:30-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like

assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Teresa E Strzelecka
Primary Examiner
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Teresa Strzelecka
6/22/07